[NOT YET SCHEDULED FOR ORAL ARGUMENT]

No. 12-5349

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

KV PHARMACEUTICAL COMPANY and THER-RX CORPORATION,

Plaintiffs-Appellants,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, ET AL.,

Defendants-Appellees.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

BRIEF FOR APPELLEES

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CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES PURSUANT TO CIR. R. 28(a)(1)

A. Parties and *Amici*

K-V Pharmaceutical Company and Ther-Rx Corporation were the plaintiffs below and are appellants here.

The United States Food and Drug Administration, Margaret Hamburg, M.D., Commissioner of Food and Drugs, the United States Department of Health and Human Services, and Kathleen Sebelius, Secretary of the United States Department of Health and Human Services, were the defendants below and are appellees here.

Alere Women's and Children's Health LLC, John P. Elliott, Michael Gordon, Michael Moretti, Jack Graham, Sue Palmer, Kenneth Higby, Peter S. Sanfilippo, Stephen Jones, Phillip Shubert, Christopher Lang, Michael Ruma, Arnold W. Cohen, Janet Ko, Rahil Malik, Joan Rosen Bloch, Norman A. Brest, Ronald J. Librizzi, Jean Payer, Jack Ludmir, A. George Neubert, Sherry Blumenthal, and Albert El-Roeiy were amici in the district court and have stated their intention to appear as amici in this Court. There were no intervenors in the district court.

B. Rulings Under Review

Appellants seek review of the Memorandum Opinion and Order entered on September 6, 2012, by the Honorable District Court Judge Amy Berman Jackson granting defendants' motion to dismiss. The district court's opinion is available on

Westlaw and at JA60. *See K-V Pharmaceutical Co. v. FDA*, 889 F. Supp. 2d 119 (D.D.C. Sept. 6, 2012).

C. Related Cases

This case was not previously before this Court or any court other than the district court. Counsel are aware of no related cases currently pending in this Court or in any other court within the meaning of Cir. R. 28(a)(1)(C). However, one of the issues in this case, concerning the FDA's discretion over drug importation under 21 U.S.C. § 381, is also presented in another case pending before this Court, *Cook v. FDA*, No. 12-5176 (D.C. Cir.).

s/ *Abby C. Wright*
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GLOSSARY

17P	Hydroxyprogesterone caproate
APA	Administrative Procedure Act
CMS	Centers for Medicare & Medicaid Services
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
JA	Joint Appendix
Pl. Br.	Plaintiffs' Brief
Q&A	Questions and Answers

STATEMENT OF JURISDICTION

Plaintiffs invoked the district court's jurisdiction under 28 U.S.C. § 1331. Complaint ¶ 30; JA21. The order under review was issued on September 6, 2012. JA60. Plaintiffs filed a notice of appeal on November 2, 2012, within the time provided by Fed. R. App. P. 4(a)(1)(B). JA10. This Court has jurisdiction under 28 U.S.C. § 1291.

STATEMENT OF THE ISSUES

The Federal Food, Drug and Cosmetic Act (FDCA or Act) imposes a variety of requirements on drug compounding activities. The Food and Drug Administration (FDA) exercises enforcement discretion with respect to certain drug compounding activities. The issues presented are the following:

(1) Whether *Heckler v. Chaney*, 470 U.S. 821 (1985), precludes judicial review of the FDA's exercise of enforcement discretion, under certain conditions, with respect to the compounding of hydroxyprogesterone caproate ("17P").

(2) Whether the FDA must refuse admission of all imports of the active pharmaceutical ingredient used to compound 17P.

PERTINENT STATUTES AND REGULATIONS

Pertinent statutes are reproduced in the addendum to this brief.

STATEMENT OF THE CASE

This case involves a challenge to FDA's exercise of enforcement discretion under the FDCA. Plaintiffs are the owner and distributor of a drug called Makena.

Makena is the trade name for a form of hydroxyprogesterone caproate, also known as "17P," that is used to prevent preterm labor in certain women. Complaint ¶ 3, JA12; ¶¶ 24-25, JA20. In February 2011, FDA approved Makena, which had previously been designated as an "orphan drug" used to treat a rare condition or disease. Complaint ¶ 8, JA14. Because Makena is an orphan drug, subject to certain exceptions, FDA may not approve another drug application for the same drug to treat the same condition for seven years from the date of Makena's approval. 21 U.S.C. § 360cc(a).

Prior to FDA's approval of Makena, doctors treated pregnant women with versions of 17P that were produced by compounding pharmacies. Complaint ¶ 9, JA15. Compounding is "a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient." *Thompson v. Western States Med. Ctr.*, 535 U.S. 357, 360-61 (2002). Plaintiffs allege that some compounding pharmacies have continued to compound 17P since Makena's approval. Compounded versions of the drug are significantly cheaper than the price at which plaintiffs offer Makena. Complaint ¶¶ 68, 71, JA32-33.

Following FDA's approval of Makena, plaintiffs sent letters to compounding pharmacies suggesting that FDA would begin undertaking enforcement action with respect to the compounding of 17P. *See* JA215-16. In March 2011, FDA issued a press release, stating that plaintiffs' letters were "not correct" and that "at this time and under this unique situation, FDA does not intend to take enforcement action against pharmacies that compound [17P] based on a valid prescription for an individually

identified patient unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile products." JA233. In June 2012, FDA issued an updated press release regarding the compounding of 17P. In the updated press release, FDA stated that it "is applying its normal enforcement policies for compounded drugs to compounded [17P]." JA274. Under those policies, FDA "generally prioritizes enforcement actions related to compounded drugs using a risk-based approach, giving the highest enforcement priority to pharmacies that compound products that are causing harm or that amount to health fraud." *Id.* FDA informed the public that compounded drugs, including compounded 17P, "do not undergo premarket review nor do they have an FDA finding of safety and efficacy." JA273. FDA further explained that "[c]ompounding large volumes of drugs that are copies of FDA-approved drugs circumvents important public health requirements, including the [FDCA's] drug approval provisions." JA273-74.

Plaintiffs brought this suit against FDA in July 2012, asserting that the March 2011 statement "effectively revoked and nullified" their orphan drug's marketing exclusivity by, in their view, encouraging compounding pharmacies to make 17P that competes with Makena. Complaint ¶¶ 77, 80, JA36-38. Plaintiffs asked the court to order FDA to "take sufficient enforcement actions to stop the unlawful competition with Makena" from pharmacies that are compounding 17P. Complaint 42, JA52. Plaintiffs also asserted that FDA is required to block importation of the active

pharmaceutical ingredient used to make compounded versions of 17P. Complaint ¶ 123, JA48.

The district court dismissed plaintiffs' suit, holding that FDA's decision not to bring enforcement actions against compounding pharmacies was an unreviewable exercise of enforcement discretion under *Heckler v. Chaney*, 470 U.S. 821 (1985). JA61. The district court further held that "the complaint is devoid of the factual allegations needed to support the conclusory assertion" that federal law required FDA to block entry of the active pharmaceutical ingredients used to make 17P. JA96.

STATEMENT OF FACTS

I. STATUTORY BACKGROUND

A. The Federal Food, Drug, and Cosmetic Act ("FDCA") regulates the manufacturing, labeling, and marketing of drugs in the United States. The Food and Drug Administration ("FDA") is charged with enforcing the FDCA.

Under the FDCA's comprehensive scheme for regulating drug manufacturing, labeling, and marketing, it is unlawful to distribute any "new drug" intended for human use in interstate commerce without FDA approval. 21 U.S.C. §§ 331(d), 355(a). To obtain FDA approval, the sponsor must show that the drug is both safe and effective for its intended uses. 21 U.S.C. §§ 355(a), (b). Drugs are also subject to the FDCA's misbranding and adulteration provisions, *see id.* §§ 351, 352, including the requirement that drugs be manufactured using "current good manufacturing practice," *see id.* § 351(a)(2)(B).

The FDCA, as amended by the Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983), provides special treatment for "orphan drugs," which are drugs intended to treat diseases or conditions affecting fewer than 200,000 people in the United States. As relevant here, when FDA approves a new drug application for an orphan drug, it "may not approve" another drug sponsor's new drug application "for such drug for such disease or condition . . . until the expiration of seven years from the date of the approval of the approved application." 21 U.S.C. § 360cc(a). FDA may, however, approve an application for the same drug to treat a different condition, or a different drug to treat the same condition. Section 360cc's exclusivity provision thus does not guarantee that an orphan drug will not face competition from other drugs treating the indicated condition or from other companies manufacturing the orphan drug for a different indication.

B. The FDCA also regulates drug importation. *See generally* 21 U.S.C. § 381. Imported drugs are subject to a variety of legal requirements, and FDA may take action to exclude drugs that do not meet those requirements. *See* 21 U.S.C. §§ 351, 352, 355, 381(a)(1)-(4).

Under the FDCA, section 381(a),[1] the Secretary of the Department of Homeland Security[2] "shall deliver to the Secretary of Health and Human Services,

[1] References in the brief to "sections" are to sections of Title 21 of the United States Code.

upon his request," samples of the product being imported or offered for import into the United States. *Id.* § 381(a). "If it appears from the examination of such samples or otherwise that," *inter alia* , the article is adulterated, misbranded, or in violation of the new drug approval requirements of 21 U.S.C. § 355, "then such article shall be refused admission . . . ." *Id.*

C. This case concerns compounded drugs. Compounding is a process in which "a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient. Compounding is typically used to prepare medications that are not commercially available, such as medication for a patient who is allergic to an ingredient in a mass-produced product." *Thompson v. Western States Med. Ctr.*, 535 U.S. 357, 360-61 (2002). Compounding may provide an important public health benefit where patients with unique needs could not otherwise be treated. *See id.* at 369 ("The Government . . . has an important interest . . . in permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs.").

Except as otherwise provided by the Act, compounded drugs are subject to the same regulatory requirements as other drugs, including the requirements for manufacturing in compliance with current good manufacturing practice and the

[2] The statute refers to the Secretary of the Treasury, but the relevant functions were transferred to the Department of Homeland Security under the Homeland Security Act. *See* 6 U.S.C. § 203.

prohibition against distributing unapproved new drugs in interstate commerce. *See generally* 21 U.S.C. §§ 321(g)(1), 321(p) (definitions of "drug" and "new drug" for purposes of FDCA), 351(a)(2)(B), 355(a); *Med. Ctr. Pharma. v. Mukasey,* 536 F.3d 383, 394, 406 (5th Cir. 2008). In 1992, FDA issued a Compliance Policy Guide that set forth its policy for enforcing the requirements of the FDCA against compounding pharmacies. As a general matter, the 1992 Guide explained that FDA would exercise enforcement discretion and abstain from bringing enforcement actions for traditional pharmacy compounding. JA98-103.

Congress amended the FDCA in 1997, through the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296. In that Act, Congress enacted 21 U.S.C. § 353a, which specifically addresses "Pharmacy compounding" of human drugs and is based largely on the 1992 Compliance Policy Guide. *See Western States*, 535 U.S. at 364.

Under section 353a, when certain statutory conditions are met, compounded drugs are explicitly exempt from three requirements of the FDCA: (i) the requirement that manufacturing methods and facilities conform to "current good manufacturing practice," 21 U.S.C. § 351(a)(2)(B); (ii) the requirement that the drug's labeling contain "adequate directions for use", *id.* § 352(f)(1); and (iii) the requirement of premarket approval, *id.* § 355. To be exempt, among other things, there must be a valid prescription for an identified individual patient and the compounding must be done by a licensed physician or pharmacist who compounds the drug using bulk drug

substances that comply with certain requirements. *Id.* § 353a(b)(1)(A). In addition, the compounder may not produce a drug that has been withdrawn from the market for safety reasons and may not "compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product." *Id.* § 353a(b)(1)(C), (D).

The criteria in section 353a include restrictions on the advertising and promotion of compounded drugs. *See id.* § 353a(a), (c). In *Western States*, the Supreme Court held that the advertising restrictions were unconstitutional, but did not rule on the severability of those restrictions from the other portions of 21 U.S.C. § 353a. *Western States*, 535 U.S. at 360. Two circuit courts have reached different conclusions on the severability issue. *Compare Western States Med. Ctr. v. Shalala,* 238 F.3d 1090, 1096 (9th Cir. 2001)*, with Med. Ctr. Pharma. v. Mukasey,* 536 F.3d 383, 401 (5th Cir. 2008).

In the wake of the Supreme Court's decision in *Western States* and the resulting uncertainty regarding the status of the statute governing compounding, FDA issued another Compliance Policy Guide in 2002. *See* Compliance Policy Guide, Sec. 460.200, "Pharmacy Compounding" (May 2002), JA161. In its 2002 guidance, FDA explained that it believed "that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing and distributing unapproved new drugs for human use in a manner that is clearly outside the bounds of traditional pharmacy practice and that violates the Act." JA163. It set forth a non-exhaustive list

of the circumstances under which it would consider enforcement action. These circumstances include pharmacies compounding drugs removed from the market for safety reasons, pharmacies using commercial scale manufacturing or testing equipment to compound drugs, pharmacies compounding drugs for third parties to resell, and pharmacies compounding drug products "that are essentially copies of commercially available FDA-approved drug products." JA163-64.

Given the conflicting circuit court opinions regarding the severability of the advertising and promotion restrictions in section 353a, there is uncertainty about the extent to which courts will apply section 353a. Thus when considering advisory actions and enforcement actions based on compounding, such as a seizure or an injunction, FDA carefully assesses the compounder's conduct under both the 2002 Compounding Compliance Policy Guide and section 353a before taking action. FDA generally prioritizes enforcement actions using a risk-based approach, giving the highest priority to compounded products that are causing harm or that amount to health fraud.

II. FACTUAL BACKGROUND

A. Hydroxyprogesterone caproate, known as "17P," was originally approved in 1956 to treat various obstetrical and gynecological conditions, including recurrent miscarriage, threatened miscarriage, and post-partum pains, and was marketed under the name Delalutin. In 1999, Bristol-Myers Squibb notified FDA that Delalutin was no longer being marketed in the United States and requested that its approved

applications be withdrawn. *See* Determination That Delalutin Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. 36,419, 36,420 (June 25, 2010). After FDA withdrew approval in 2000, there was no FDA-approved version of 17P available in the United States. Doctors continued, however, to treat pregnant women with 17P available through compounding pharmacies. Complaint ¶ 9, JA15.

In 2006, FDA received a new drug application from plaintiffs' predecessor in interest for approval of 17P, under the trade name of Makena (then called "Gestiva"), to prevent preterm birth in singleton pregnancies. Complaint ¶ 50, JA27. In January 2007, FDA designated Makena an orphan drug. Complaint ¶ 51, JA27. In 2011, FDA approved Makena to reduce the risk of preterm birth in "women with a singleton pregnancy who have a history of singleton spontaneous preterm birth." Complaint ¶¶ 3, 55, 66, JA12, 28, 31.

Following FDA approval, plaintiffs set the initial list price for a dose of Makena at $1,500. Complaint ¶ 68, JA32. Makena is administered by weekly injection; thus, the original list price for a course of treatment of Makena was up to $30,000. Complaint ¶ 73, JA34. Compounded doses of 17P were available for significantly cheaper.

B. Following FDA's approval of Makena, plaintiffs, apparently concerned about competition from compounded versions of 17P, sent letters to compounding pharmacies stating that continuing to compound 17P "renders the compounded

product subject to FDA enforcement for violating certain provisions of the [FDCA], as well as FDA guidance," JA215.

On March 30, 2011, FDA issued a statement regarding Makena. FDA noted that 17P had been available through compounding pharmacies for many years and that the agency generally had "exercised enforcement discretion with respect to most products made through traditional pharmacy compounding," including 17P. JA233. The agency emphasized that "[b]ecause Makena is a sterile injectable, where there is a risk of contamination, greater assurance of safety is provided by an approved product," as opposed to a compounded product. *Ibid.* FDA further explained that it "prioritizes enforcement actions related to compounded drugs using a risk-based approach, giving the highest enforcement priority to pharmacies that compound products that are causing harm or that amount to health fraud." *Ibid.*

FDA explained that Makena's manufacturer "has sent letters to pharmacists indicating that FDA will no longer exercise enforcement discretion with regard to compounded versions of Makena. This is not correct." FDA then stated that "[i]n order to support access to this important drug, at this time and under this unique situation," it did not intend to take enforcement action against pharmacies compounding 17P "based on a valid prescription for an individually identified patient unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile

products." *Ibid.* FDA reiterated that it could "at any time revisit a decision to exercise enforcement discretion." *Ibid.*

Plaintiffs began their own testing program of compounded versions of 17P, *see* Complaint ¶ 5, JA13-14, and, in October 2011, plaintiffs provided FDA with the results of their tests of samples of compounded 17P products and samples of the active pharmaceutical ingredients used to compound 17P. JA251. FDA reviewed the data and issued a statement in November 2011 announcing that, although FDA had not validated or otherwise confirmed the analyses provided by plaintiffs, the information submitted showed that "there is variability in the purity and potency of both the bulk [active pharmaceutical ingredients] and compounded [17P] products that were tested." *Ibid.* FDA further stated that the agency was conducting its own investigation and would also conduct an on-site review of the laboratory analyses provided by plaintiffs. *Ibid.*

FDA further reminded physicians and patients that "before approving the Makena new drug application, FDA reviewed manufacturing information, such as the source of the [active pharmaceutical ingredient] used by its manufacturer, proposed manufacturing processes, and the firm's adherence to current good manufacturing practice." *Ibid.* FDA echoed its March statement: "as with other approved drugs, greater assurance of safety and effectiveness is generally provided by the approved product than by a compounded product." *Ibid.*

On June 15, 2012, FDA issued a statement summarizing the results of its investigation of compounded 17P products. JA273. After testing samples of the active pharmaceutical ingredients used to compound 17P and samples of the finished compounded products, and also re-testing the retained samples of compounded 17P from plaintiffs' investigation, FDA concluded that it had not identified any major safety problems. JA273. The agency again explained that "[a]lthough the analysis of this limited sample . . . did not identify any major safety problems, approved drug products, such as Makena, provide a greater assurance of safety and effectiveness than do compounded products." *Ibid.* The agency stressed that, by contrast, compounded versions of 17P "are not FDA approved, which means they do not undergo premarket review nor do they have an FDA finding of safety and efficacy." *Ibid*

In the June 2012 statement, FDA also addressed the issue of pharmacy compounding of copies of Makena. FDA explained that "[c]ompounding large volumes of drugs that are copies of FDA-approved drugs circumvents important public health requirements, including the [FDCA's] drug approval provisions." JA273-74. The agency emphasized that "one factor" it considers "in determining whether a drug may be compounded is whether the prescribing practitioner has determined that the product is necessary for the particular patient and would provide a significant difference for the patient as compared to the FDA-approved commercially available drug product." *Ibid.* The June

statement "emphasize[d] that [FDA] is applying its normal enforcement policies for compounded drugs to compounded [17P]." *Id.* FDA also warned compounding pharmacies that "[t]he compounding of any drug, including [17P], should not exceed the scope of traditional pharmacy compounding." *Id.*

Plaintiffs issued their own press release in response to FDA's June 15, 2012 statement. Among other things, plaintiffs trumpeted FDA's statement that it is "applying its normal enforcement policies for compounded drugs to compounded [17P]." K-V Press Release, "FDA and CMS Issue Important Updates on Makena," (June 18, 2012), *available at* http://www.kvph.com/news_center_article.aspx?articleid=359 (emphasis added and quotation marks omitted), *last viewed* May 9, 2013. Plaintiffs stated that this was "a *reversal* of [FDA's] March 30, 2011 statement." *Ibid* (emphasis added).

On June 29, 2012, FDA added a Questions and Answers (Q&As) section to its web page. JA277. Among other things, the Q&As reiterated that "FDA does not consider compounding large volumes of copies, or what are essentially copies, of any approved commercially-available drug to fall within the scope of traditional pharmacy practice"; that "FDA may take enforcement action against pharmacies that compound large volumes of drugs that are essentially copies of commercially available products and for which there does not appear to be a medical need for individual patients to whom the drug is dispensed"; and that "FDA's June 15, 2012 statement should not be interpreted to mean that the FDA will take enforcement action only if the agency

identifies a particular safety problem. We reiterate that the compounding of any drug, including [17P], should not exceed the scope of traditional pharmacy compounding." JA277-78. Plaintiffs thereafter issued a press release describing FDA's March 30, 2011, statement as "outdated." See K-V Press Release, "FDA Issues Further Guidance About Makena," (July 2, 2012), *available at* http://www.kvph.com/news_center_article.aspx?articleid=362, *last viewed* May 10, 2013.

III. PRIOR PROCEEDINGS

Notwithstanding FDA's June 2012 announcement that compounding of 17P would be subject to FDA's normal enforcement policies, plaintiffs filed suit against FDA on July 5, 2012, under the Administrative Procedure Act ("APA"). Plaintiffs alleged that FDA's March 2011 Statement and its supposed "policy of non-enforcement against the compounding of 17P," JA48, "effectively revoked and nullified Plaintiffs' statutory right to a period of seven years of market exclusivity." Complaint ¶ 77, JA36. Plaintiffs sought "temporary, preliminary, and permanent declaratory and injunctive relief" against FDA to stop the "unlawful competition with Makena" from compounded 17P. Complaint ¶ 102, JA43; Complaint 42, § 5(b), JA52. Specifically, plaintiffs asked the district court to order FDA to withdraw the March 2011 and June 2012 statements; to "take sufficient enforcement actions" to "stop the unlawful competition"; and to make periodic reports to the court describing the enforcement actions the agency was undertaking. Complaint 42, § 5, JA52-53.

Plaintiffs further alleged that FDA was violating 21 U.S.C. § 381(a) by not refusing admission to the active pharmaceutical ingredient used to compound 17P when it is offered for importation into the United States. Complaint ¶ 123, JA48. Plaintiffs requested the court to order FDA to bar entry into the United States of any future shipment of foreign-manufactured active pharmaceutical ingredients for compounding "non-customized" 17P. Complaint 42, § 5(d), JA52.

The government moved to dismiss the complaint, arguing that under *Heckler v. Chaney*, 470 U.S. 821, 828 (1985), FDA's decisions regarding whether to bring enforcement actions against compounding pharmacies and its decisions not to refuse admission for the imported 17P active pharmaceutical ingredients were not subject to judicial review.[3]

The district court granted the government's motion to dismiss in September 2012, holding that plaintiffs' claims regarding FDA's statements "challenge FDA's discretionary enforcement activities and therefore assert unreviewable claims." JA61. The court further held that plaintiffs' importation claim failed to state a claim under Fed. R. Civ. P. 12(b)(6).

The court began by recognizing that "[i]n essence, what plaintiffs challenge is defendants' failure to take enforcement action" against pharmacies compounding 17P.

[3] The government also argued that plaintiffs lacked standing. The court rejected that argument, holding that plaintiffs have standing. The court determined it "likely" that FDA enforcement mechanisms would result in a reduction of the amount of compounded 17P on the market. JA73.

JA67. The court explained that *Chaney* therefore controlled the case, and FDA's lack of enforcement was not subject to judicial review under the APA. JA75. The court examined and rejected each of the bases on which plaintiffs urged that Congress had circumscribed FDA's authority.

First, the court determined that the Orphan Drug Act, 21 U.S.C. § 360cc, and the pharmacy compounding provision, 21 U.S.C. § 353a, did not "require[] FDA to proceed against unlawful compounders—they don't say a word about it." JA79. Moreover, the court noted that plaintiffs' counsel "repeatedly failed to direct the Court to any statutory provision that would satisfy the *Chaney* test and overcome the presumption." JA79.

The court also rejected plaintiffs' argument that their claims were reviewable under *Crowley v. Caribbean Transport, Inc.*, 37 F.3d 671 (D.C. Cir. 1994), in which this Court suggested that, in contrast to a particular enforcement decision, "an agency's statement of a *general enforcement policy* may be reviewable for legal sufficiency where the agency has expressed the policy as a formal regulation after the full rulemaking process . . . or has otherwise articulated it in some form of universal policy statement." JA82 (quoting *Crowley*, 37 F.3d at 676). The district court determined that the "March Statement is neither the formal result of a rulemaking process nor a universal policy statement." JA82.

The court then concluded that even if the March 2011 Statement were reviewable as a general enforcement policy, it had been superseded by FDA's June

2012 Statement. JA89. The court rejected plaintiffs' argument that FDA had demonstrated a policy of non-enforcement through lack of enforcement. The court explained that "[t]his argument simply serves to demonstrate the basic deficiency in the complaint: the fact that plaintiffs are challenging an FDA decision (or series of decisions) not to initiate enforcement action." JA90.

The court then turned to plaintiffs' importation claim and held that plaintiffs had failed to state a valid claim for relief. Because plaintiffs conceded that "FDA's decision as to a particular article offered for import . . . is within FDA's enforcement discretion," they could not bring a claim regarding FDA's enforcement decisions as to any particular shipment of the active ingredient in 17P. JA94-95 (quoting Plaintiffs' Opposition at 33, n.34),. Moreover, the court noted that plaintiffs' complaint failed to point to any FDA policy statement regarding enforcement against importation of 17P active pharmaceutical ingredients. JA92.

SUMMARY OF ARGUMENT

Plaintiffs want the federal courts to compel FDA to take enforcement actions against pharmacies compounding 17P that is not customized to meet the particular medical needs of a particular patient. That demand for judicial intervention in FDA enforcement decisions is foreclosed by the Supreme Court's decision in *Heckler v. Chaney*. In *Chaney*, the Court held that "an agency's decision not to prosecute or enforce, whether through civil or criminal process, is a decision generally committed to an agency's absolute discretion," and that "the presumption that agency decisions

not to institute proceedings are unreviewable under 5 U.S.C. § 701(a)(2) is not overcome by the enforcement provisions of the FDCA." 470 U.S. at 831, 837. The district court therefore correctly dismissed plaintiffs' suit under *Chaney*.

Plaintiffs' brief is a fruitless quest for grounds on which to distinguish *Chaney*. The requirements of 21 U.S.C. § 360cc, which governs orphan drug approval, provide no basis for a different outcome here. FDA has not violated the terms of section 360cc, and that section provides no guidelines for how FDA should exercise enforcement discretion. Nor does plaintiffs' reliance on this Court's decision in *Crowley* advance their claim. FDA's superseded statement of enforcement discretion regarding 17P compounding is no more amenable to judicial review than the FDA enforcement policy regarding off-label use of drugs in executions in *Chaney*, and unlike the scenario discussed in *Crowley*, plaintiffs have not argued that FDA's statement of enforcement discretion rests on an erroneous interpretation of a legal command.

Plaintiffs' attempt to deprive FDA of its enforcement discretion with respect to imported drugs fares no better. As plaintiffs admitted in the district court, FDA has discretion to determine the actions it will take with respect to particular shipments of unapproved drugs. Although plaintiffs now assert that FDA must block every shipment of the active pharmaceutical ingredient of 17P on the ground that it is an unapproved drug, that claim founders on the language of section 381(a) and Congress's clear intention to allow compounding of drugs from imported active pharmaceutical ingredients when specified conditions are met.

STANDARD OF REVIEW

This Court reviews the district court's grant of a motion to dismiss de novo. *Piersall v. Winter*, 435 F.3d 319, 321 (D.C. Cir. 2006). Like the district court, this Court reviews the agency's interpretation of the statute it is charged with administering under the standard set out in *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984). *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1278-80 (D.C. Cir. 2004).

ARGUMENT

I. PLAINTIFFS' SUIT IS FORECLOSED BY *HECKLER V. CHANEY*.

A. Under *Heckler v. Chaney*, FDA's Decision Whether To Take Enforcement Actions Against Pharmacies Compounding 17P Is Committed to Agency Discretion.

Heckler v. Chaney, 470 U.S. 821 (1985), like this case, involved a challenge to FDA's exercise of enforcement discretion under the FDCA. In *Chaney*, a group of prison inmates sentenced to death by lethal injection sought to compel FDA to take enforcement actions to prevent the introduction of an approved drug into interstate commerce for an unapproved use in violation of the FDCA's approval and misbranding provisions. 470 U.S. at 823-24. In response, FDA explained that its jurisdiction with respect to approved drugs used in lethal injection was in some doubt, but, in any event, should not be exercised to interfere with state criminal justice systems. It further explained its enforcement practices in the area of unapproved uses of approved drugs: "Generally, enforcement proceedings in this area are initiated only

when there is a serious danger to the public health or a blatant scheme to defraud. We cannot conclude that those dangers are present under State lethal injection laws . . . ." *Chaney*, 470 U.S. at 824-25 (internal quotation marks omitted).

The Supreme Court determined that the agency's decision not to take enforcement action against drugs used for lethal injection was unreviewable, noting "the general unsuitability for judicial review of agency decisions to refuse enforcement." *Id.* at 831. The Court noted that it had "recognized on several occasions over many years that an agency's decision not to prosecute or enforce, whether through civil or criminal process, is a decision generally committed to an agency's absolute discretion." *Id.*

The Court recited a number of reasons for concluding that decisions not to enforce generally fall outside the scope of judicial review. As the Court explained, "an agency decision not to enforce often involves a complicated balancing of a number of factors which are peculiarly within its expertise," including "whether agency resources are best spent on this violation or another" and "whether the particular enforcement action requested best fits the agency's overall policies." *Id.* The Court thus recognized that the "agency is far better equipped than the courts to deal with the many variables involved in the proper ordering of its priorities." *Id.* at 831-32.

In their complaint in this case, plaintiffs ask the court to order FDA to rescind its March 2011 and June 2012 statements and "not maintain or implement the policy of non-enforcement as to non-customized compounding of 17P"; to "take sufficient

enforcement actions to stop the unlawful competition with Makena by compounded 17P not customized to meet the special needs of patients"; to make quarterly reports to the district court regarding "actions they have taken to terminate shipments of non-customized compounded 17P"; and to block the importation of the active pharmaceutical ingredient used to make non-customized 17P. JA52-53.

These are precisely the types of enforcement actions that the Supreme Court held to be "committed to an agency's absolute discretion" in *Chaney*. 470 U.S. at 831. FDA's statements reflect exactly the kind of balancing of factors that the Supreme Court listed in *Chaney*: "whether agency resources are best spent on this violation or another" and "whether the particular enforcement action requested best fits the agency's overall policies." As FDA explained in both the March 2011 and June 2012 Statements, FDA generally prioritizes enforcement for compounded drugs using a "risk-based approach" which gives the highest priority to issues of safety and health fraud. JA233, JA274.

This Court's decisions confirm that FDA's enforcement decisions are committed to agency discretion. In *Jerome Stevens*, for example, this Court held that FDA's exercise of enforcement discretion was unreviewable even though it related to the distribution of multiple manufacturers' versions of a particular type of unapproved new drug and was announced in several notices published in the Federal Register. *Jerome Stevens Pharm. Inc. v. FDA,* 402 F.3d 1249, 1258 (D.C. Cir. 2005). And in *Schering*, this Court held that the government's decision to enter into a settlement agreement to

not engage in further enforcement proceedings pending other events was an unreviewable exercise of enforcement discretion. *Schering Corp. v. Heckler*, 779 F.2d 683, 686 (D.C. Cir. 1985). Plaintiffs devote only a footnote to their efforts to distinguish *Jerome Stevens* and *Schering*, arguing that the agency's exercise of enforcement discretion in those cases was for a limited period of time. Pl. Br. 39 n.55. But they provide no reason why the duration of discretion is dispositive, and, in any event, the limited exercise of enforcement discretion related to compounding of 17P described in FDA's March 2011 statement was superseded by FDA's June 2012 statement.

B. *Chaney's* Presumption of Non-Reviewability Is Fully Applicable in This Case.

1. The considerations set forth in *Chaney* apply in this case.

None of plaintiffs' reasons for arguing that *Chaney*'s presumption is rebutted hold force. Pl. Br. 41-42. They first urge that "FDA's Statement does not invoke any factor *Chaney* identified as indicative of enforcement discretion in individual cases." Pl. Br. 42. But both the March 2011 and June 2012 statements indicate that FDA employs a risk-based approach that prioritizes certain enforcement actions, which is precisely the type of determination regarding the best use of an agency's limited resources that *Chaney* recognized is committed to agency discretion by law. *Chaney*, 470 U.S. at 831. *See* JA233, JA274. The June 2012 Statement further affirms that FDA "is applying its normal enforcement policies for compounded drugs to compounded [17P]."

JA274. Insofar as the March 2011 Statement said that FDA did not intend to take enforcement actions against pharmacies that compound 17P under certain, limited conditions, FDA has since made clear that it is applying its normal enforcement policies to compounded 17P and that "[t]he compounding of any drug, including [17P], should not exceed the scope of traditional pharmacy compounding." *Id.*; *see also* JA277-78 (Q&A). Thus, contrary to plaintiffs' suggestion, FDA is not pursuing a "policy of non-enforcement" regarding the compounding of 17P.

Plaintiffs' claim that the rationales of the Supreme Court's decision in *Chaney* do not apply here because FDA's actions may affect their ability to sell Makena is equally without merit. Pl. Br. 42. FDA's actions in *Chaney* affected the manner in which states could carry out executions. The question is not whether enforcement action has an effect, or the magnitude of that effect, but whether Congress has constrained the agency's exercise of discretion. As the Supreme Court explained in *Chaney,* if Congress has not "indicated an intent to circumscribe agency enforcement discretion," and not "provided meaningful standards for defining the limits of that discretion . . . then an agency refusal to institute proceedings is a decision 'committed to agency discretion by law.'" *Chaney*, 470 U.S. at 834-35. Plaintiffs' reliance on *Ctr. For Auto. Safety v. Dole*, 828 F.2d 799, 803 (D.C. Cir. 1987), thus does not advance their claim. In that case, this Court found "law to apply" in an agency's binding regulations,

which removed discretion to proceed based on the agency's usual enforcement policies. No such regulations are present here.

2. 21 U.S.C. § 360cc does not provide "law to apply."

Plaintiffs next urge that section 360cc provides a "judicially manageable standard[]" for this Court to apply in reviewing FDA's enforcement decision, and that the presumption that enforcement decisions are not reviewable thus does not apply in this case. Pl. Br. 43 (quoting *Chaney*, 470 U.S. at 830). But that reliance is wholly misplaced. Plaintiffs have not—and cannot— assert that FDA has violated section 360cc, which provides no guidelines with respect to the exercise of FDA's enforcement discretion.[4]

Section 360cc outlines specific conditions under which FDA may not approve a new drug application under section 355 or license a biological product under the Public Health Service Act. 21 U.S.C. § 360cc. The statute's language is plain, and prohibits only the approval of an application for the same drug (here, 17P) to treat the

[4] Plaintiffs suggest in passing that section 355 and 353a might provide law to apply. Pl. Br. 47. The Supreme Court rejected reliance on the former provision in *Chaney* itself. *Chaney*, 470 U.S. at 835-36 ("These provisions are simply irrelevant to the agency's discretion to refuse to initiate proceedings."); *see also Cutler v. Hayes*, 818 F.2d 879, 893 (D.C. Cir. 1987) (the FDCA "imposes no clear duty upon FDA to bring enforcement proceedings to effectuate either the safety or the efficacy requirements of the Act"). Section 353a sets forth conditions under which drugs may be compounded for human use by licensed pharmacists or physicians without having to comply with certain of the FDCA's requirements. When a compounded drug does not comply with those requirements, however, it is section 355 that provides the basis for enforcement, and, as discussed, section 355 does not provide law to apply.

same condition (certain pregnant women at risk for preterm labor). Plaintiffs have not asserted that FDA violated the statute's terms. It did not. Instead, eschewing a "literal" reading of the statute (Pl. Br. 45) in favor of the provision's supposed "thrust" (Pl. Br. 44), they claim that FDA's March statement is the "functional equivalent" (Pl. Br. 43) of an approval.

As an initial matter, to the extent that the March 2011 statement may have suggested that FDA would not take enforcement action against pharmacies compounding 17P under certain circumstances, it addressed plaintiffs' assertion that FDA *would* be taking enforcement action, and the June 2012 statement makes clear that FDA is applying its normal enforcement priorities with respect to 17P. Moreover, FDA's statements were not the "functional equivalent" of FDA approving another application for 17P to treat preterm labor. FDA made clear in its statements that compounded versions of 17P were *not* approved drug products and did not come with the "assurance of safety" that comes from an approved drug product. JA233, JA273-74.

Moreover, this Court has previously rejected a similar exhortation to view the FDCA's exclusivity provisions in "functional" and non-literal terms, rejecting a pharmaceutical company's claim that FDA's failure to take action against a generic version of a drug undermined a grant of exclusivity. In *Teva Pharm. Indus. Ltd. v. Crawford*, 410 F.3d 51 (D.C. Cir. 2005), a pharmaceutical company challenged FDA's response to a citizen petition requesting that FDA prohibit Pfizer, Inc., from

marketing an "authorized generic" version of its own brand name drug, which did not require FDA approval. Under the FDCA, Teva received 180 days of exclusivity for being the first drug maker to challenge Pfizer's patent, and FDA was thus prohibited from approving another generic version of the drug during this period. *Id.* at 52 (citing 21 U.S.C. § 355(j)(5)(B)(iv)). Pfizer's authorized generic "competed directly with Teva's [generic gabapentin] during [Teva's] period of exclusivity," and Teva argued that this Court should adopt a "functional" and non-literal interpretation of the statute to protect its market exclusivity. *Id.* at 52-53.

This Court squarely rejected that argument. FDA had not violated the terms of the statute, and this Court determined that the provision could not be read to limit "what the FDA may do in such a way as to prevent the holder of an approved [new drug application]. . . from marketing a brand-generic product." *Id.* at 54. The same is true here: Section 360cc is entirely silent as to whether and under what conditions FDA should or must take enforcement action against compounded or unapproved versions of the same drug that may exist. FDA has not violated the statute, which does not "provide[] guidelines for the agency to follow in exercising its enforcement powers. " *Chaney*, 470 U.S. at 833. The *Chaney* presumption against review applies.

This Court's decision in another case involving Teva Pharmaceuticals does not counsel a different outcome. *See Teva Pharma. USA v. Sebelius*, 595 F.3d 1303, 1318 (D.C. Cir. 2010) (cited at Pl. Br. 45 n.59). That case did not involve enforcement discretion, but related to FDA's authority under the statute to remove a patent from a

list of patents applicable to an approved drug, which would have the effect of removing the entitlement to exclusivity for the first generic manufacturer to have challenged the patent. *Id.* at 1304. The question was whether the statute permitted FDA to "delist" the patent; it did not involve the question whether FDA could be compelled to take particular enforcement actions.

C. FDA's Enforcement Decisions Do Not Fall Outside the *Chaney* Framework.

1. This Court's decision in *Crowley* does not advance plaintiffs' claim.

As a basis for asserting that *Chaney* does not preclude this Court's review, plaintiffs claim that FDA's March 2011 statement "announces a general policy." Pl. Br. 30. They interpret this Court's decision in *Crowley* as holding that statements of general enforcement policy, as distinct from case-specific enforcement decisions, are subject to judicial review notwithstanding *Chaney*. But *Crowley* holds nothing of the sort.

To begin, plaintiffs' suggestion that FDA's March 2011 Statement is reviewable because it is a "general policy" runs headlong into the Supreme Court's decision in *Chaney*. In its March 2011 Statement, FDA explained that at that particular time "FDA does not intend to take enforcement action against pharmacies that compound [17P] based on a valid prescription for an individually identified patient unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile

products." JA233. *Chaney* involved an equally "general" statement on enforcement: "Generally, enforcement proceedings in this area are initiated only when there is a serious danger to the public health or a blatant scheme to defraud. We cannot conclude that those dangers are present under State lethal injection laws . . . ." *Chaney*, 470 U.S. at 824-25 (internal quotation marks omitted). The Supreme Court held that this statement was not subject to review, even though the exercise of enforcement discretion involved the adoption of a uniform approach to a class of drugs rather than "a single-shot decision." *See* Pl. Br. 30.

Crowley suggests that statements of broad enforcement policy are "more likely to be direct interpretations of the commands of the substantive statute," which render them more amenable to judicial review and correction than "the sort of mingled assessments of fact, policy, and law . . . that are, as [*Heckler v. Chaney*] recognizes, peculiarly within the agency's expertise and discretion." 37 F.3d at 677. As plaintiffs note (Pl. Br. 31-32), this Court has reviewed agency interpretations of legal commands that may affect an agency's enforcement discretion. *See OSG Bulk Ships, Inc. v. United States*, 132 F.3d 808 (D.C. Cir. 1998) (reviewing agency interpretation of statute to authorize release of certain vessels into domestic market and upholding interpretation); JA84 (district court's discussion of the case). In such a case the relief a court can grant is clear: the court may correct legal error, and an agency may then exercise any relevant enforcement discretion without the impediment of a misconception of the agency's legal authority to act.

Here, in contrast, none of FDA's statements set forth an interpretation of the FDCA, and plaintiffs have presented no persuasive claim of legal error in those statements. Plaintiffs are not asking the courts to review the FDA's interpretation of its governing statute, but rather to direct specific enforcement actions to be taken against third parties. This is precisely the type of relief foreclosed by *Chaney*.

Crowley also suggests that "an agency's pronouncement of a broad policy against enforcement" in the form of a "universal policy statement" is potentially amenable to judicial review. 37 F.3d at 676-77. But here, FDA did not purport to articulate a universal policy statement against enforcing 21 U.S.C. § 355 or other statutory provisions applicable to drug compounding. As the district court correctly explained, "the March Statement is neither the formal result of a rulemaking process nor a universal policy statement, so the limited circumstances that [this Court] said *may* call for a different result are not present here." JA82. And, as the district court correctly recognized, the March 2011 Statement does not differ in any relevant way from the FDA statement regarding its enforcement against lethal injection drugs in *Chaney,* and it does not represent a disavowal of "an intention to proceed against compounding pharmacies as a general matter." JA83.

In any event, FDA revisited the March 2011 statement in subsequent press releases and letters, and it is now, as plaintiffs recognize, "outdated." *See* K-V Press Release, "FDA Issues Further Guidance About Makena," (July 2, 2012), *available at* http://www.kvph.com/news_center_article.aspx?articleid=362. FDA's June 2012

Statement makes clear that FDA is "applying its normal enforcement policies for compounded drugs to compounded [17P]." JA274. The same was made clear to Wedgewood Pharmacy in a letter that reiterated that "FDA does not view compounding large volumes of drugs that are copies of FDA-approved drugs as traditional pharmacy compounding." JA280. Thus, plaintiffs have not identified *any* current policy with which they disagree. Plaintiffs' real quarrel is not with a supposed "policy of non-enforcement," but rather with the fact that FDA has set its enforcement priorities in a way that focuses on safety and health fraud, not necessarily on reducing competition with Makena.[5] That is precisely the kind of weighing of enforcement priorities that *Chaney* is meant to insulate from judicial intervention.

2. FDA has not abdicated its statutory responsibility, and *Adams v. Richardson* has no application in this case.

Much of plaintiffs' argument in their brief centers on their view that FDA has "solicited" illegal conduct. From this they argue that FDA has abdicated its statutory responsibilities and that *Chaney* therefore has no application.

To begin, this argument cannot be squared with the facts of *Chaney* itself. In *Chaney*, FDA had declared that it would not take enforcement action against certain

[5] To that end, FDA recently has been focusing its resources on high-priority inspections of about 30 firms, identified using a risk-based model, to assess their sterile drug production practices. *See* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm347722.htm.

drugs used for lethal injection. *See* 470 U.S. at 824-25 ("Were FDA clearly to have jurisdiction in the area, moreover, we believe we would be authorized to decline to exercise it under our inherent discretion to decline to pursue certain enforcement matters. . . . Generally, enforcement proceedings in this area are initiated only when there is a serious danger to the public health or a blatant scheme to defraud.") (quoting FDA's statement). In both *Chaney* and here, *see* Pl. Br. 24, FDA made its enforcement decisions against the backdrop of ongoing conduct on the part of third parties (the states in *Chaney*; private parties here).

Second, plaintiffs have no basis to assert that compounding of 17P after March 2011 "would not have occurred if FDA had done nothing." Pl. Br. 25 (underlining omitted). In no sense was "FDA's issuance of a press release . . . the equivalent of an order or license." Pl. Br. 27 (underlining omitted). FDA's since-superseded March statement did not authorize, solicit, or call forth unlawful compounding.

Finally, plaintiffs' reliance on this Court's decision in *Adams v. Richardson*, 480 F.2d 1159 (D.C. Cir. 1973) (en banc), misses the mark. Pl. Br. 36-41, 49-51. In *Adams*, plaintiffs challenged the Department of Health, Education, and Welfare's ongoing funding of segregated schools. This Court determined that in actively providing funds to racially discriminatory institutions, the agency had abdicated its statutory responsibilities. *Adams*, 480 F.2d at 1162; *see also Chaney*, 470 U.S. at 833 n.4 (citing *Adams*); JA87 n.14 (noting that the Supreme Court expressed no view on whether *Adams* remained good law under *Chaney*). As this Court later explained, the case

involved a provision that "explicitly directed all federal departments and agencies distributing federal funds to effectuate the provision of the Act prohibiting racial discrimination in programs accepting such funds." *Cutler v. Hayes*, 818 F.2d 879, 893 (D.C. Cir. 1987). There is no similarly mandatory provision here, and this case is fundamentally different from a case in which an agency funds segregated institutions in direct contravention of federal law.[6] As this Court explained in *Cutler,* the FDCA "imposes no clear duty upon FDA to bring enforcement proceedings to effectuate either the safety or the efficacy requirements of the Act." *Ibid.*

Even assuming FDA's enforcement decisions with respect to compounding pharmacies were subject to judicial review—which they are not—those decisions in no way amount to an abdication of statutory duties. Instead FDA has prioritized, as it must, certain enforcement activities. As explained in both the March 2011 and June 2012 statements, FDA employs a risk-based approach that generally prioritizes certain enforcement actions: specifically, those concerning safety and public health fraud. *See* JA233, JA274. Moreover, when plaintiffs brought information to FDA's attention suggesting problems in the potency and purity of compounded 17P and its active pharmaceutical ingredients, FDA promptly conducted its own investigation and testing. JA273. FDA also issued an import bulletin to the agency's import program

[6] In June 2012, the Centers for Medicare and Medicaid Services reminded "States of their responsibility to cover FDA approved products, such as Makena, that qualify as covered outpatient drugs under the Medicaid drug rebate program." JA275.

managers requesting "heightened alert, and careful examination of" the active pharmaceutical ingredient for 17P. JA253-54 (requesting, for example, evaluation of "[e]ntry documentation and product labeling" for "compliance with drug import requirements," such as "firm registration and product listing requirements.").

FDA has also repeatedly told the public that "approved drug products, such as Makena, provide greater assurance of safety and effectiveness than do compounded products." JA273; *see also* JA277. FDA has warned compounding pharmacies that "[t]he compounding of any drug, including [17P], should not exceed the scope of traditional pharmacy compounding." JA277. FDA also specifically warned Wedgewood Pharmacy that its interpretation of FDA's statements was erroneous. *See* JA279 ("We are writing to ensure that Wedgewood Pharmacy is not operating under the misimpression that there is a 'green light' large volumes of copies of Makena."). Moreover, FDA has been investigating compounding pharmacies that are posing a risk to patient safety. *See* Sun and Kindy, *FDA inspects specialty compounding pharmacies in targeted action* (March 1, 2013), *available* at http://articles.washingtonpost.com/2013-03-01/national/37368259_1_pharmacies-drug-evaluation-inspection. Even if this Court were to consider FDA's actions with respect to the compounding of 17P, there is simply no comparison to the agency action reviewed in *Adams*.

Nor is it any answer to argue that FDA has abdicated its duty "not to subvert the grant of orphan drug exclusivity" under 21 U.S.C. § 360cc(a). Pl. Br. 37.[7] As explained, FDA has not violated that statute, which prohibits FDA from granting another new drug application for the same drug to treat the same condition. Nor does it assist plaintiffs to rely on 21 U.S.C. § 393(b), which provides FDA's mission statement. As plaintiffs acknowledge (Pl. Br. 38 n.53), this Court has concluded that this provision does not provide guidelines for the exercise of discretion. *See Jerome Stevens Pharms*, 402 F.3d at 1258.

3. The relief plaintiffs seek puts this case squarely within the *Chaney* framework.

Plaintiffs claim that the relief they seek "would not intrude into the zone of enforcement discretion protected by *Chaney*," claiming, for example, that "FDA would choose the enforcement strategy tactics, tools, and methods. The preservation of FDA's discretion as to individual cases follows from the fact that the challenge here is to an FDA policy, not to an FDA decision in an individual enforcement case." Pl. Br. 28, 29. Plaintiffs urge that the relief they seek would be "to undo the unlawful

[7] Plaintiffs also advert to a due process challenge to FDA's actions in footnote 3 of their brief. Pl. Br. 3. Plaintiffs urge that the district court erred in finding waiver. But plaintiffs raised the issue in only a cursory fashion in the district court, and have only mentioned it in a footnote in their brief without elaborating on the claim. Plaintiffs have thus failed to raise the issue for this Court's review. *See Wash. Legal Clinic for the Homeless v. Barry*, 107 F.3d 32, 39 (D.C. Cir. 1997).

Statement's harmful consequences" and that the reports to the district court they seek are "merely" an "incentive" for FDA to achieve that objective. Pl. Br. 28.

Plaintiffs are wrong: in light of the June 2012 Statement that plaintiffs acknowledged as a "reversal" of the March 2011 Statement,[8] it is plain that the only relief that would satisfy plaintiffs is for FDA to forgo its enforcement priorities and target compounding pharmacies that compound 17P. Indeed, FDA is currently focusing its resources on high-priority inspections of certain firms—identified using a risk-based model—to assess their sterile drug production practices as part of the agency's effort to ensure sterility of compounded products. *See* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm347722.htm. Plaintiffs ask this Court to order FDA to divert its limited resources away from such actions in order to identify and bring actions against pharmacies that compound "unlawful, uncustomized" 17P. This is precisely the type of relief foreclosed by *Chaney*. This Court's decisions in *Cobell v. Norton*, 240 F.3d 1081, 1108 (D.C. Cir. 2001), and *Ind. & Mich. Elec. Co. v. Fed. Power Comm'n*, 502 F.2d 336 (D.C. Cir. 1974) (cited at Pl. Br. 51), do not advance plaintiffs' argument. Those cases did not involve an agency's enforcement discretion or order an enforcement program against third parties.

[8] *See* K-V Press Release, "FDA and CMS Issue Important Updates on Makena," (June 18, 2012), *available at* http://www.kvph.com/news_center_article.aspx?articleid=359.

Plaintiffs' contention that "[t]he relief KV seeks is within the scope of the types of relief approved in *Adams,*" even if true, would make no difference. Pl. Br. 50. Plaintiffs have wholly failed to show that they fall within the narrow exception carved out by this Court in *Adams v. Richardson*; they are thus entitled to no relief from this Court. Indeed, plaintiffs' reliance on *Adams v. Richardson* serves as a tacit acknowledgment that they seek to force FDA to take specific enforcement actions.

II. FDA HAS ENFORCEMENT DISCRETION WITH RESPECT TO IMPORTATION OF ACTIVE PHARMACEUTICAL INGREDIENTS.

A. Section 381(a) Imposes No Mandatory Duty.

Plaintiffs renew their arguments on appeal that the importation of the active pharmaceutical ingredients used to compound 17P is prohibited by section 381(a) and that FDA was compelled to take action to block importation. Pl. Br. 52-56.[9] Under Section 381(a), as described above, the Secretary of the Department of Homeland Security "shall deliver to the Secretary of Health and Human Services, upon his request," samples of the product being imported or offered for import into the United States. *Id.* § 381(a). "If it appears from the examination of such samples or otherwise that . . . (3) such article is adulterated, misbranded, or in violation of [21 U.S.C. § 355] . . . then such article shall be refused admission . . . ." 21 U.S.C. § 381(a).

[9] This Court is considering the issue of FDA's enforcement discretion with respect to section 381(a) in *Cook v. FDA*, No. 12-5176 (D.C. Cir.), argued before Judges Rogers, Ginsburg, and Sentelle on March 25, 2013.

As the district court pointed out, plaintiffs conceded below that "'FDA's decision as to a particular article offered for import, like its decision as to enforcement against a particular company in a particular factual setting, is within FDA's enforcement discretion.'" JA92 (quoting Pls. Opp. at 33 n.34). That concession is fundamentally at odds with their position on appeal that "if FDA's automated system discloses that a new drug is unapproved and therefore appears to be in violation, FDA has no discretion to admit the article." Pl. Br. 53. Plaintiffs have also failed to identify what final agency action they challenge with respect to importation: they have identified no particular shipment of 17P that they are challenging nor any statement or order of FDA that allows for a particular shipment or even all shipments to enter. The district court therefore "struggle[d] to find any 'final agency action' to review here." *See* JA93 n.19.

In any event, plaintiffs' interpretation of section 381(a) is incorrect. Nothing in the language of section 381(a) reflects any decision by Congress to override the general presumption that administrative agencies have discretion to determine the circumstances under which they will take enforcement action.

1. The language of section 381(a) lends no support to plaintiffs' argument, and use of the word "shall" in that section does not remove FDA's enforcement discretion. *Chaney* itself exemplifies the error of attaching too much weight to a single use of the word "shall" in the enforcement context. *Chaney* involved a criminal provision that "state[d] baldly that any person who violates the Act's substantive

prohibitions 'shall be imprisoned . . . or fined.'" *Chaney*, 470 U.S. at 835 (quoting 21 U.S.C. § 333). The Supreme Court rejected the proposition that "this language, which is commonly found in the criminal provisions of Title 18 of the United States Code," operates to "mandate[] criminal prosecution of every violator of the Act." *Id.*

Accordingly, when words like "shall" are used in the enforcement context, they are ordinarily not interpreted to impose an inflexible mandate that prohibits the agency from determining that no enforcement action is warranted. Rather, they apply in those individual circumstances in which the agency has elected to initiate action. As the Fifth Circuit has explained, for example, while "'shall' is normally interpreted to impose a mandatory duty . . . when duties within the traditional realm of prosecutorial discretion are involved, the courts have not found this maxim controlling." *City of Seabrook v. Costle*, 659 F.2d 1371, 1374 n.3 (5th Cir. 1981). Numerous other cases are to the same effect. *See, e.g., Dubois v. Thomas*, 820 F.2d 943, 946-47 (8th Cir. 1987) (finding in context of Federal Water Pollution Control Act that the word "shall" did not impose a mandatory duty to bring an enforcement action, and collecting cases reaching same result); *Wood v. Herman*, 104 F. Supp. 2d 43, 47 (D.D.C. 2000) ("While it is a recognized tenet of statutory construction that the word 'shall' is usually a command, this principle has not been applied in cases involving administrative enforcement decisions." (citation omitted)).

Here, moreover, even if the word "shall" were interpreted to be other than permissive, the statute would not impose an inflexible mandate on FDA to undertake

enforcement action in every case. The third sentence of Section 381(a) does not say that FDA "shall" take action whenever certain conditions are satisfied. Rather, the "shall be refused admission" language describes the consequences that follow if FDA makes a determination that "it appears" that one of the Act's requirements has been violated. Before any article is refused admission, FDA affords the "owner or consignee . . . an opportunity to introduce testimony . . . relevant to the admissibility of the article . . . orally or in writing." 21 C.F.R. § 1.94(a).

Under 21 U.S.C. § 381(a), FDA may trigger the statute by determining that it "appears" that the statutory conditions have been satisfied. The agency's final notice of remedial action is typically preceded by a series of steps, including a notice to the importer stating that the product appears to be violative and offering an opportunity to introduce testimony or recondition the product. *See* 21 C.F.R. § 1.94. The language of section 381(a) does not constrain the agency's discretion on the antecedent question whether to make a determination that it appears that a statutory obligation has been violated and begin the enforcement process, and thus does not mandate enforcement action against every possible violator of the FDCA. *See Her Majesty the Queen v. U.S. Environmental Protection Agency*, 912 F.2d 1525 (D.C. Cir. 1990) (recognizing that particular statutory duties were only triggered by formal findings).

Cont'l Seafoods, Inc. v. Schweiker, 674 F.2d 38, 42-43 (D.C. Cir. 1982), is not to the contrary, as there FDA *had* made the requisite determination. Pl. Br. 52-53. Nor does *Kreis v. Sec'y of Air Force*, 866 F.2d 1508, 1513 (D.C. Cir. 1989), advance plaintiffs'

claim. This Court expressly distinguished between the existence of an objective fact and "the Secretary's determination that such conditions are present." *Ibid.*; *see also Southwest Airlines Co. v. Transp. Sec. Agency*, 650 F.3d 752, 756 (D.C. Cir. 2011) (noting "the distinction between the objective existence of certain conditions and the [agency]'s determination that such conditions are present, stressing that a statute phrased in the latter terms fairly exudes deference to the [agency].") (internal quotation marks omitted) (alterations in original).

2 .When FDA is presented with an import of an active pharmaceutical ingredient that is labeled for use in compounding—whether 17P or any other drug—FDA does not, absent other considerations, typically seek to bar the importation on the ground that it is an unapproved new drug, provided that the ingredient is one that could be used for compounding under the agency's 2002 Compounding compliance guide or 21 U.S.C. § 353a.[10] This is so even though, for example, the active pharmaceutical ingredients imported to make 17P are unapproved new drugs in violation of section 355.[11]

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[10] FDA's decisions about import entries for the active pharmaceutical ingredients of 17P are exercises of enforcement discretion under section 381(a) and are unrelated to the March 2011 statement. As the District Court noted, the March 2011 Statement "does not even mention the import of components of compounded 17P. The only subjects of the statement are the 'pharmacies that compound' 17P." JA 92.

[11] The active pharmaceutical ingredient imported for the manufacture of Makena is covered by Makena's new drug application.

Plaintiffs' request for a declaration that 17P active pharmaceutical ingredients "cannot lawfully be . . . imported" because they are unapproved "new drugs," Complaint 41, JA51, if granted, would effectively prohibit all compounding of 17P, even when fully compliant with section 353a. Plaintiffs' position must be rejected because Congress expressly intended to permit (under the conditions defined in section 353a) compounding from bulk drug substances (i.e., active pharmaceutical ingredients). Indeed, in section 353a, Congress expanded the bulk drug substances that would be available for compounding. *Compare* FDA's 1992 Compliance Guide, § 7132.16, JA101 ("If a pharmacy compounds finished drugs from bulk active ingredient materials considered to be unapproved new drug substances, . . . such activity must be covered by" an investigational new drug application.), *with* 21 U.S.C. § 353a(b)(1)(A)(i), (d)(2) (permissible bulk drug substances include those listed in a United States Pharmacopeia or National Formulary monograph, components of drugs approved by FDA, and those included on a list that Congress authorized FDA to develop by regulation). More importantly, in section 353a, Congress expressly permitted compounding with bulk drug substances that are manufactured in a "foreign establishment that is registered" with FDA. *See* 21 U.S.C. § 353a(b)(1)(A)(ii). And, indeed, approximately 80% of all manufacturers of active pharmaceutical ingredients registered with FDA are located outside this country. *See* FDA Special Report, "Pathway to Global Product Safety and Quality" at 2, *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices

/OfficeofGlobalRegulatoryOperationsandPolicy/GlobalProductPathway/UCM262528.pdf. To accept plaintiffs' position that all such active pharmaceutical ingredients must be refused admission would thus directly undermine congressional intent.

B. Plaintiffs' Attempt To Square Their Reading of Section 381(a) with Section 353a Must Be Rejected.

Plaintiffs recognize, as they must, that FDA may admit *some* unapproved active pharmaceutical ingredients for use in compounding. Indeed, they propose that FDA could hold hearings on each batch of imported active pharmaceutical ingredients for 17P to "assess the owners' or consignees' responses as to whether the compounding of the [17P] would comply with 21 U.S.C. § 353a." Pl. Br. 55. At base, thus, plaintiffs seek to control the manner in which FDA exercises its discretion to take enforcement action against imported bulk substances. That claim is squarely foreclosed by *Heckler v. Chaney*.

These assertions underscore that plaintiffs' goal in this lawsuit is to replace FDA's exercise of its discretion with their own. In so doing, plaintiffs wholly ignore the substantial outlay of resources such a process would entail for FDA and the practical difficulties inherent in such an approach. Instead, plaintiffs baldly assert that hearings "need not consume substantial FDA resources." Pl. Br. 54 n.66. But plaintiffs' arguments apply to all unapproved active pharmaceutical ingredients used in compounded drugs, and to conduct hearings every time a company seeks to import *any* active pharmaceutical ingredient for use by a compounding pharmacy, as plaintiffs

urge, would impose a substantial burden on FDA and consume limited agency resources that the agency would otherwise expend in line with its enforcement priorities. *See* Pl. Br. 54 n.66. As the Supreme Court in *Chaney* made clear, decisions about how best to use resources are committed to agency discretion by law. *See Chaney*, 470 U.S. at 831.

Moreover, FDA would often be unable to determine through a hearing conducted under 21 C.F.R. § 1.94(a) whether a given shipment of 17P active pharmaceutical ingredient will be used to compound drugs that meet the conditions in section 353a. Most active pharmaceutical ingredients intended for pharmacy compounding are imported by distributors who may not know the circumstances under which the finished products will ultimately be compounded. For example, the importer may not know whether the pharmacists to whom the importer distributes the active pharmaceutical ingredient will always receive a valid prescription for an identified individual patient for the compounded drug product. *See* 21 U.S.C. § 353a(a).

Most importantly, however, plaintiffs' approach misunderstands the interaction of section 353a and section 381(a). Even if FDA were to determine that the active pharmaceutical ingredient offered for importation would be compounded under the conditions in section 353a, the active pharmaceutical ingredient would still be an unapproved new drug subject to refusal under 21 U.S.C. § 381(a). As FDA explained in its briefs in the district court, section 353a does not exempt active pharmaceutical

ingredients from compliance with any provision of the Act. These ingredients are new drugs, and they are unapproved. Section 353a exempts compounded "drug products" from sections 351(a)(2)(B), 352(f)(1), and 355, but it offers no exemption to the ingredients used to make them. 21 U.S.C. § 353a(a). "Drug product" is a term of art, defined by FDA and understood to mean the finished dosage form of a drug. *See, e.g.,* 21 C.F.R. § 314.3 ("Drug product means a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients."); 21 C.F.R. § 320.1(b) (same).[12]

Because the exemptions in section 353a only apply to "drug products" and not the active pharmaceutical ingredients used to make them, if section 381(a) is read in the mandatory manner in which plaintiffs suggest, FDA would be required to refuse admission to all unapproved active pharmaceutical ingredients for use in compounding of any drug, regardless of the impact on public health or other considerations, and regardless of whether FDA holds hearings under 21 C.F.R. § 1.94.

[12] The meaning of "drug product" is likewise plain in the context of section 353a. The statute provides that sections 351(a)(2)(B), 352(f)(1), and 355 "shall not apply to a drug product if the drug product is compounded for an identified individual patient based on . . . a valid prescription . . . " under specified conditions. 21 U.S.C. § 353a(a). Physicians write prescriptions for—and pharmacists compound—the finished dosage form of a drug, not its active pharmaceutical ingredient. Moreover, a "drug product," is compounded from its ingredients. *See id.* § 353a(b)(1) ("drug product may be compounded under subsection (a) if the licensed pharmacist or physician . . . compounds the drug product using bulk drug substances" that fall into one of three categories and uses other "ingredients" that "comply with the standards of an applicable" monograph).

And contrary to plaintiffs' suggestion (Pl. Br. 48 n.60), a listing under section 353a(d)(2) is ineffective to provide an exemption, because that subsection merely allows FDA to list bulk substances that may be used in compounding; it does not convert a bulk substance into a "drug product" exempt from section 355.

Plaintiffs' mandatory reading of section 381(a) would also deprive FDA of the means to effectively address drug shortages by exercising its enforcement discretion to not refuse entry to medically necessary drugs in a time of shortage. Plaintiffs urge that FDA might be able to exercise some other statutory and regulatory mechanisms to alleviate drug shortages, including—in their view—granting investigational new drug applications. *See* Pl. Br. 48 n.60. But FDA cannot address all drug shortages through investigational new drug applications.[13]

[13] For example, plaintiffs cite 21 C.F.R. § 312.320, but FDA's treatment investigational new drug application and protocol regulations provide that such investigational new drug applications and protocols are only available, inter alia, when (1) the drug is being investigated in a controlled clinical trial under an investigational new drug application designed to support a marketing application for the expanded access use, or all clinical trials of the drug have been completed, and (2) the manufacturer is pursuing a marketing application for the expanded access use. 21 C.F.R. § 312.320(a)(1)&(2). Plaintiffs also cite FDA regulations addressing intermediate-size expanded access investigational new drug applications and protocols, 21 C.F.R. § 312.315, which may, in some cases, be used in the situation of a drug shortage. However, they are not intended or sufficient for drug shortage situations affecting large numbers of patients. *See ibid.* Moreover, the availability of an intermediate-size expanded access investigational new drug application or protocol to address a given drug shortage depends, inter alia, on whether there is a sponsor willing to submit an application or protocol and comply with investigational new drug application requirements. *See id.* § 312.305(b)&(c)(2), 312.315(c)&(d)(2).

Moreover, there is no basis for plaintiffs' suggestion that a shortage could be adequately addressed by a provision that applies only to the reimportation of drugs that were originally manufactured in the United States, 21 U.S.C. § 381(d)(2), or by provisions applicable only during national security crises, *id.* § 360bbb-3. *See* Pl. Br. 48 n.60. Drug shortages cannot always be addressed with drugs originally manufactured in the United States, and do not always occur during national security crises. FDA's enforcement discretion with respect to imported drugs is necessary to preserve its ability to respond to drug shortages.

Faced with the absurd results of their interpretation of section 381(a), it is thus no wonder that plaintiffs conceded in district court that "'FDA's decision as to a particular article offered for import . . . is within FDA's enforcement discretion.'" JA92 (quoting Pls. Opp. at 33 n.34). As explained, that concession is correct; and it only serves to underscore that the gravamen of plaintiffs' complaint is that the court must order FDA to exercise its discretion to take enforcement action against particular import entries of 17P. Plaintiffs' claims are thus barred under *Chaney*.

CONCLUSION

The judgment of the district court should be affirmed.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH FEDERAL RULE OF APPELLATE PROCEDURE 32(A)

I hereby certify that this brief complies with the requirements of Fed. R. App. P. 32(a)(5) and (6) because it has been prepared in 14-point Garamond, a proportionally spaced font.

I further certify that this brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because it contains 11,735 words excluding the parts of the brief exempted under Rule 32(a)(7)(B)(iii), according to the count of Microsoft Word.

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CERTIFICATE OF SERVICE

I hereby certify that on May 13, 2013, I electronically filed the foregoing brief with the Clerk of the Court for the United States Court of Appeals for the District of Columbia Circuit by using the appellate CM/ECF system. I further certify that I will cause eight paper copies of this brief to be filed with the Court within two business days.

The participants in the case are registered CM/ECF users and service will be accomplished by the appellate CM/ECF system.

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ADDENDUM

Addendum Contents

21 U.S.C. § 353a

(a) In general

Sections 351(a)(2)(B), 352(f)(1), and 355 of this title shall not apply to a drug product if the drug product is compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, if the drug product meets the requirements of this section, and if the compounding--

(1) is by--

(A) a licensed pharmacist in a State licensed pharmacy or a Federal facility, or

(B) a licensed physician,

on the prescription order for such individual patient made by a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or

(2)(A) is by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient; and

(B) is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product, which orders have been generated solely within an established relationship between--

(i) the licensed pharmacist or licensed physician; and

(ii)(I) such individual patient for whom the prescription order will be provided; or

(II) the physician or other licensed practitioner who will write such prescription order.

(b) Compounded drug

(1) Licensed pharmacist and licensed physician

A drug product may be compounded under subsection (a) of this section if the licensed pharmacist or licensed physician--

(A) compounds the drug product using bulk drug substances, as defined in regulations of the Secretary published at section 207.3(a)(4) of title 21 of the Code of Federal Regulations--

(i) that--

(I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

(II) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or

(III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (d) of this section;

(ii) that are manufactured by an establishment that is registered under section 360 of this title (including a foreign establishment that is registered under section 360(i) of this title); and

(iii) that are accompanied by valid certificates of analysis for each bulk drug substance;

(B) compounds the drug product using ingredients (other than bulk drug substances) that comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

(C) does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective; and

(D) does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product.

(2) Definition

For purposes of paragraph (1)(D), the term "essentially a copy of a commercially available drug product" does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug product.

(3) Drug product

A drug product may be compounded under subsection (a) only if--

(A) such drug product is not a drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product; and

(B) such drug product is compounded in a State--

(i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or

(ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

The Secretary shall, in consultation with the National Association of Boards of Pharmacy, develop a standard memorandum of understanding for use by the States in complying with subparagraph (B)(i).

(c) Advertising and promotion

A drug may be compounded under subsection (a) of this section only if the pharmacy, licensed pharmacist, or licensed physician does not advertise or promote the compounding of any particular drug, class of drug, or type of drug. The pharmacy, licensed pharmacist, or licensed physician may advertise and promote the compounding service provided by the licensed pharmacist or licensed physician.

(d) Regulations

(1) In general

The Secretary shall issue regulations to implement this section. Before issuing regulations to implement subsections (b)(1)(A)(i)(III), (b)(1)(C), or (b)(3)(A) of this section, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopoeia, pharmacy, physician, and consumer organizations, and other experts selected by the Secretary.

(2) Limiting compounding

The Secretary, in consultation with the United States Pharmacopoeia Convention, Incorporated, shall promulgate regulations identifying drug substances that may be used in compounding under subsection (b)(1)(A)(i)(III) of this section for which a monograph does not exist or which are not components of drug products approved by the Secretary. The Secretary shall include in the regulation the criteria for such substances, which shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify.

(e) Application

This section shall not apply to--

(1) compounded positron emission tomography drugs as defined in section 321(ii) of this title; or

(2) radiopharmaceuticals.

(f) "Compounding" defined

As used in this section, the term "compounding" does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling.

21 U.S.C. § 360cc

(a) Exclusive approval, certification, or license

Except as provided in subsection (b) of this section, if the Secretary--

(1) approves an application filed pursuant to section 355 of this title, or

(2) issues a license under section 262 of Title 42

for a drug designated under section 360bb of this title for a rare disease or condition, the Secretary may not approve another application under section 355 of this title or issue another license under section 262 of Title 42 for such drug for such disease or condition for a person who is not the holder of such approved application or of such license until the expiration of seven years from the date of the approval of the approved application or the issuance of the license. Section 355(c)(2) of this title does not apply to the refusal to approve an application under the preceding sentence.

(3) Redesignated (2)

(b) Exceptions

If an application filed pursuant to section 355 of this title is approved for a drug designated under section 360bb of this title for a rare disease or condition or if a license is issued under section 262 of Title 42 for such a drug, the Secretary may, during the seven-year period beginning on the date of the application approval or of the issuance of the license, approve another application under section 355 of this title or issue a license under section 262 of Title 42, for such drug for such disease or condition for a person who is not the holder of such approved application or of such license if--

(1) the Secretary finds, after providing the holder notice and opportunity for the submission of views, that in such period the holder of the approved application or of the license cannot assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated; or

(2) such holder provides the Secretary in writing the consent of such holder for the approval of other applications or the issuance of other licenses before the expiration of such seven-year period.

21 U.S.C. § 381

§ 381. Imports and exports

(a) Imports; list of registered foreign establishments; samples from unregistered foreign establishments; examination and refusal of admission

The Secretary of the Treasury shall deliver to the Secretary of Health and Human Services, upon his request, samples of food, drugs, devices, tobacco products, and cosmetics which are being imported or offered for import into the United States, giving notice thereof to the owner or consignee, who may appear before the Secretary of Health and Human Services and have the right to introduce testimony. The Secretary of Health and Human Services shall furnish to the Secretary of the Treasury a list of establishments registered pursuant to subsection (i) of section 360 or section 387e(h) of this title and shall request that if any drugs, devices, or tobacco products manufactured, prepared, propagated, compounded, or processed in an establishment not so registered are imported or offered for import into the United States, samples of such drugs, devices, or tobacco products be delivered to the Secretary of Health and Human Services, with notice of such delivery to the owner or consignee, who may appear before the Secretary of Health and Human Services and have the right to introduce testimony. If it appears from the examination of such samples or otherwise that (1) such article has been manufactured, processed, or packed under insanitary conditions or, in the case of a device, the methods used in, or the facilities or controls used for, the manufacture, packing, storage, or installation of the device do not conform to the requirements of section 360j(f) of this title, or (2) such article is forbidden or restricted in sale in the country in which it was produced or from which it was exported, or (3) such article is adulterated, misbranded, or in violation of section 355 of this title, or prohibited from introduction or delivery for introduction into interstate commerce under section 331(*ll*) of this title, or (4) the recordkeeping requirements under section 2223 of this title (other than the requirements under subsection (f) of such section) have not been complied with regarding such article, then such article shall be refused admission, except as provided in subsection (b) of this section. With respect to an article of food, if importation of such food is subject to, but not compliant with, the requirement under subsection (q) that such food be accompanied by a certification or other assurance that the food meets applicable requirements of this chapter, then such article shall be refused admission. If such article is subject to a requirement under section 379aa or 379aa-1 of this title and if the Secretary has credible evidence or information indicating that the responsible person (as defined in such section 379aa or 379aa-1 of this title) has not complied with a requirement of such section 379aa or 379aa-1 of this title with respect to any such article, or has not allowed access to records described in such section 379aa or

379aa-1 of this title, then such article shall be refused admission, except as provided in subsection (b) of this section. The Secretary of the Treasury shall cause the destruction of any such article refused admission unless such article is exported, under regulations prescribed by the Secretary of the Treasury, within ninety days of the date of notice of such refusal or within such additional time as may be permitted pursuant to such regulations. Clause (2) of the third sentence of this paragraph shall not be construed to prohibit the admission of narcotic drugs the importation of which is permitted under the Controlled Substances Import and Export Act, except that the Secretary of Health and Human Services may destroy, without the opportunity for export, any drug refused admission under this section, if such drug is valued at an amount that is $2,500 or less (or such higher amount as the Secretary of the Treasury may set by regulation pursuant to section 1498(a)(1) of Title 19 and was not brought into compliance as described under subsection (b).. The Secretary of Health and Human Services shall issue regulations providing for notice and an opportunity to appear before the Secretary of Health and Human Services and introduce testimony, as described in the first sentence of this subsection, on destruction of a drug under the sixth sentence of this subsection. The regulations shall provide that prior to destruction, appropriate due process is available to the owner or consignee seeking to challenge the decision to destroy the drug. Where the Secretary of Health and Human Services provides notice and an opportunity to appear and introduce testimony on the destruction of a drug, the Secretary of Health and Human Services shall store and, as applicable, dispose of the drug after the issuance of the notice, except that the owner and consignee shall remain liable for costs pursuant to subsection (c). Such process may be combined with the notice and opportunity to appear before the Secretary and introduce testimony, as described in the first sentence of this subsection, as long as appropriate notice is provided to the owner or consignee.

(b) Disposition of refused articles

Pending decision as to the admission of an article being imported or offered for import, the Secretary of the Treasury may authorize delivery of such article to the owner or consignee upon the execution by him of a good and sufficient bond providing for the payment of such liquidated damages in the event of default as may be required pursuant to regulations of the Secretary of the Treasury. If it appears to the Secretary of Health and Human Services that (1) an article included within the provisions of clause (3) of subsection (a) of this section can, by relabeling or other action, be brought into compliance with this chapter or rendered other than a food, drug, device, or cosmetic, or (2) with respect to an article described in subsection (a) relating to the requirements of sections 379aa or 379aa-1 of this title,, the responsible person (as defined in section 379aa or 379aa-1 of this title) can take action that would assure that the responsible person is in compliance with section 379aa or 379aa-1 of

this title, as the case may be, final determination as to admission of such article may be deferred and, upon filing of timely written application by the owner or consignee and the execution by him of a bond as provided in the preceding provisions of this subsection, the Secretary may, in accordance with regulations, authorize the applicant, or, with respect to clause (2), the responsible person, to perform such relabeling or other action specified in such authorization (including destruction or export of rejected articles or portions thereof, as may be specified in the Secretary's authorization). All such relabeling or other action pursuant to such authorization shall in accordance with regulations be under the supervision of an officer or employee of the Department of Health and Human Services designated by the Secretary, or an officer or employee of the Department of the Treasury designated by the Secretary of the Treasury.

(c) Charges concerning refused articles

All expenses (including travel, per diem or subsistence, and salaries of officers or employees of the United States) in connection with the destruction provided for in subsection (a) of this section and the supervision of the relabeling or other action authorized under the provisions of subsection (b) of this section, the amount of such expenses to be determined in accordance with regulations, and all expenses in connection with the storage, cartage, or labor with respect to any article refused admission under subsection (a) of this section, shall be paid by the owner or consignee and, in default of such payment, shall constitute a lien against any future importations made by such owner or consignee.

. . .

(o) Registration statement

If an article that is a device is being imported or offered for import into the United States, and the importer, owner, or consignee of such article does not, at the time of offering the article for import, submit to the Secretary a statement that identifies the registration under section 360(i) of this title of each establishment that with respect to such article is required under such section to register with the Secretary, the article may be refused admission. If the article is refused admission for failure to submit such a statement, the article shall be held at the port of entry for the article, and may not be delivered to the importer, owner, or consignee of the article, until such a statement is submitted to the Secretary. Subsection (b) of this section does not authorize the delivery of the article pursuant to the execution of a bond while the article is so held. The article shall be removed to a secure facility, as appropriate. During the period of time that such article is so held, the article shall not be transferred by any person from

the port of entry into the United States for the article, or from the secure facility to which the article has been removed, as the case may be.